

### **REMARKS/ARGUMENTS**

The Notice of Non-Compliant Amendment dated November 29, 2005 has been received and reviewed. This response is directed to that Notice.

Applicants respectfully request reconsideration and allowance of this application in view of the amendments above and the following comments. Claims 1-22 were pending. By this Amendment, claims 1, 3-4 and 20-22 have been amended, and claims 2, and 5-19 have been canceled without prejudice or disclaimer. Claim 24 is new. Support for this claim can be found in the specification on page 1, lines 4-6. It is believed that no new matter has been added.

#### **Notice of Non-Compliant Amendment**

The Examiner issued a notice of non-compliant amendment in response to the applicant's submission dated September 23, 2005 which was included with a Request for Continued Examination. The Examiner stated that the claims as amended in the applicant's response were directed to claims that are independent or distinct from the invention originally claimed and elected. Accordingly, applicants have submitted amended claims in this response that are directed to the invention as elected in a prior response. Applicants therefore respectfully request that the Examiner enter the present amendments and consider said amendments in conjunction with the foregoing remarks.

#### **Claim Rejections- 35 U.S.C. §112**

The Examiner rejected the claims because the specification was non-enabling for a method of treating cachexia in a patient with liver cirrhosis by administering an effective amount of any compound that is able to reduce the production, adsorption ore effect of endotoxin. The

Examiner stated, however, that the specification was enabling for a method of inhibiting endotoxin-mediated cytokine production in patients with cachexia by administering ursodeoxycholic acid. Accordingly, claim 1 has been amended to claim a method for treating and ameliorating endotoxin-mediated cachexia in a human patient by administering an effective amount of ursodeoxycholic acid. In addition, attached is **Exhibit 1**, which shows an experiment conducted in human patients treating patients with cachexia. Also attached is **Exhibit A**, which is a declaration by the inventor of the claimed invention. As stated in the declaration by the inventor, the experiment attached as **Exhibit 1** was conducted based on the teachings of the specification.

The Examiner further rejected claim 6 as indefinite for failing to provide proper antecedent basis for the term "bile acid". Claim 6 has been cancelled in this response, thus obviating this rejection.

Furthermore, the Examiner rejected claims 1-6 and 19-22 as containing new matter. Specifically, the Examiner stated that the term "human patient" is not supported by the specification. Rather, only the term "patient" is properly supported. Applicants respectfully submit that one skilled in the art would know that the term "patient" can mean a "human patient." In support of this, documents are attached which show that the term "patient" can mean a "human patient." It is, therefore, respectfully requested that the Examiner reconsider and withdraw this rejection.

**Claim Rejections- 35 U.S.C. §102**

The Examiner rejected claims 1-6 and 19-20 as being anticipated by U.S. Patent 5,639,744, as evidenced by U.S. Patent 4,377,595 and/or U.S. Patent 4,898,879.

In order show anticipation, the reference must teach or suggest every element of the claimed invention. These references fail to teach or suggest (as in independent amended claim 1) a method for determining, ameliorating, and treating endotoxin-mediated cachexia in a human patient by administering to the human patient a therapeutically effective amount ursodeoxycholic acid. In particular, these references fail to teach or suggest treating endotoxin-mediated cachexia with ursodeoxycholic acid.

Further, the US Patent '744 is simply directed to a synthetic compound providing amides between ursodeoxycholic acid (UDCA) and cyclic amino acids, which can be used in therapy of the biliary calculosis of cholesterol and of the pathologies caused by cholestasis. In addition, as being disclosed in the description of US Patent '744, the synthesis of the amide bondage between UDCA and the cyclic amino acid requires an enormous workload. In contrary, the inventive method for ameliorating endotoxin-mediated cachexia teaches that ordinary UDCA is sufficient for the inventive purpose and no further synthesis steps are required. US Patent '595 simply discloses administering of tyrosine and/or phenylalanine and/or other neutral amino acids to a patient with depression to increase the level of norepinephrine which is released into synapses. In US Patent '595 only a vague association of amino acids and cachexia is given and ursodeoxycholic acid is not even mentioned. Similarly, US Patent '879 only discloses a composition for administration to a patient having liver disease, comprising a cysteine free mixture of nonessential and essential amino acids. No cachexia, body wasting or UDCA is also mentioned in US Patent '879.

It is, therefore, respectfully requested that the Examiner reconsider and withdraw this rejection.

The Examiner additionally rejected claims 1-6 and 19-21 as being anticipated by U.S. Patent 6,251,884 as evidenced by U.S. Patent 4,377,595 and/or U.S. Patent 4,898,879.

U.S. Patent '884 is simply directed to a pharmacologically acceptable composition including a sulfate of UDCA and a pharmacologically acceptable carrier for treating a liver disease or an inflammatory condition of the gastrointestinal tract in a mammal. However, the synthesis of a UDCA sulfate presumes a huge expense and purification procedure, and is not comparable to the easily realizable method of using common UDCA in the applied invention. Beyond this, no cachexia or endotoxin/LPS or measuring the level of a cytokine or an inflammatory marker or its production in the blood of the patient is mentioned in US Patent '884 as in amended independent claim 1. The '595 and '879 patents were previously discussed above. Thus, these references do not anticipate the claimed invention.

It is, therefore, respectfully requested that the Examiner reconsider and withdraw this rejection.

The Examiner rejected claims 1-6 and 19 as being anticipated by U.S. Patent 5,869,265 as evidenced by U.S. Patent 4,377,595 and/or U.S. Patent 4,898,879.

US Patent '265 only describes a general concept for the treatment of liver cirrhosis, primary biliary cirrhosis, sclerosing cholangitis and other diseases which block the normal secretion of bile acids by the liver by the use of UDCA. Beyond this, no cachexia or

endotoxin/LPS or measuring the level of a cytokine or an inflammatory marker or its production in the blood of the patient is mentioned in US Patent '265 as in amended independent claim 1. The '595 and '879 patents were previously discussed above. Thus, these references do not anticipate the claimed invention.

It is, therefore, respectfully requested that the Examiner reconsider and withdraw this rejection.

Claim Rejection- 35 U.S.C. §103(a)

The Examiner rejected claims 1-6 and 19-22 as being obvious over U.S. Patent 6,251,884 or U.S. Patent 5,869,265 or U.S. Patent 5,639,744 each in view of U.S. Patent 4,377,595 and/or U.S. Patent 4,898,879.

In response, applicants assert that these references individually or combined do not teach or suggest every element of the claimed invention. As stated above, these combined references fail to teach or suggest (as in independent amended claim 1) a method for determining, ameliorating, and treating endotoxin-mediated cachexia in a human patient by administering to the human patient a therapeutically effective amount of ursodeoxycholic acid. In particular, these combined references fail to teach or suggest treating endotoxin-mediated cachexia with ursodeoxycholic acid and fail to disclose a connection between cachexia, cytokines, LPS, and ursodeoxycholic acid. Furthermore, there is no teaching or suggestion in the reference/s of a connection between cachexia, cytokines, LPS, and ursodeoxycholic acid. Accordingly, a person of ordinary skill in the art would not have the requisite motivation to combine the references.

It is, therefore, respectfully requested that the Examiner reconsider and withdraw this rejection.

Based on the foregoing remarks it is believed that the claim is in condition for allowance. However, should any issue(s) of a minor nature remain, the Examiner is respectfully requested to telephone the undersigned at telephone number (212) 808-0700 so that the issue(s) might be promptly resolved.

Based on the foregoing remarks it is believed that the claim is in condition for allowance. However, should any issue(s) of a minor nature remain, the Examiner is respectfully requested to telephone the undersigned at telephone number (212) 808-0700 so that the issue(s) might be promptly resolved.

**CONDITIONAL PETITION FOR EXTENSION OF TIME**

If entry and consideration of the amendments above requires an extension of time, Applicants respectfully request that this be considered a petition therefor. The Assistant Commissioner is authorized to charge any fee(s) due in this connection to Deposit Account No. 14-1263.

**ADDITIONAL FEE**

Please charge any insufficiency of fees, or credit any excess, to Deposit Account No. 14-1263.

Respectfully submitted,

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